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Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review

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Keywords:	Protocol, scoping review, JAK/STAT pathway, immune-mediated inflammatory skin diseases, PRISMA

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1 Protocol

2 **BMJ Open**

3 **Title:** Drugs targeting the JAK/STAT pathway for the treatment of immune-
4 mediated inflammatory skin diseases: protocol for a scoping review

5 **Short title:** Scoping review of JAK/STAT blockade in dermatology

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30 **ABSTRACT**

31 **Introduction.** The JAK/STAT pathway is known to be involved in inflammatory
32 and neoplastic skin diseases, like psoriasis, atopic dermatitis, alopecia areata,
33 vitiligo, and melanoma. Improved knowledge of the components of this pathway
34 has allowed the development of drugs, which act by inhibiting the pathway,
35 blocking specific components. This offers new therapeutic opportunities.
36 Although evidence on the use of JAK/STAT blockades in dermatological
37 diseases is growing, none have been approved for use in treating skin diseases.
38 The aim of this study is to develop an *a priori* protocol to broadly review the
39 available evidence on the use of drugs targeting the JAK/STAT pathway in the
40 treatment of dermatological diseases.

41 **Methods and analysis.** For the conduction of the scoping review protocol, we
42 will employ an established scoping review methodology described in the Joanna
43 Briggs Institute manual. This methodology outlines a 5-stage approach: 1) identify
44 the research question; 2) identify relevant studies; 3) select studies; 4) chart the data;
45 and 5) collate, summarize, and report the results, with an optional consultation exercise.
46 Finally, we used the Preferred Reporting Items for Systematic Reviews and Meta-
47 Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the
48 results.

49 **Ethics and dissemination.** Since this is a review of the literature, ethics approval is
50 not indicated. We will disseminate the findings from this study in publications in peer-
51 reviewed journals as well as presentations at relevant national and international conferences.

52 **Keywords:** Protocol; scoping review; JAK/STAT pathway; immune-mediated
53 inflammatory skin diseases; PRISMA.

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54 **Article summary**

55 **Strengths and limitations of this study**

56 ▪ Strengths of this study include the importance of unrevealing uncertainty about
57 evidence of using drugs targeting JAK/STAT pathway when prescribed as
58 *off-label* for dermatological diseases in the clinical setting.

59 ▪ We will use an established scoping review methodology, a systematic search
60 developed by two health sciences librarians, and systematic screening and
61 data abstraction carried out in duplicate.

62 ▪ A limitation of this review is the potential to miss relevant articles, especially in
63 the grey literature. To mitigate this, we will screen meeting abstracts to
64 identify any missed articles describing case reports not published in journals
65 and scanning reference lists of included articles and similar reviews.

66 INTRODUCTION

67 Improving knowledge of the molecular biology of the cell, and its adaptation to
68 the disease pathogenesis, have allowed the design of new drugs directed
69 against key targets in signaling pathway regulation. In this sense, the Janus
70 kinases (JAKs) and Signal Transducer and Activator of Transcription (STATs)
71 proteins (JAK/STAT) pathway is one of a handful of pleiotropic routes used to
72 transduce multiple extracellular signals involved in cell proliferation,
73 differentiation, migration, and apoptosis.¹ Alterations in the regulation of this
74 process have been associated with pathological events fundamentally related to
75 immunomodulatory and neoplastic (mainly hematological) disorders. In addition,
76 they have been related to the pathophysiology of several dermatological
77 diseases. Therefore, drugs that act on the JAK/STAT pathway represent an
78 opportunity for the treatment of these disorders.²

79 The JAK family is comprised by four types of cytoplasmic tyrosine kinases:
80 JAK1, JAK2, JAK3, and Tyk2.³ STAT, of which there are seven different
81 subtypes (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT 5b, and STAT6), is
82 the other fundamental component of the cascade⁴. After being phosphorylated
83 by JAK, STAT translocates to the nucleus to induce the transcription of specific
84 genes. Different types of ligands, from cytokines, such as interleukins (IL), to
85 hormones, such as erythropoietin, activate this pathway to produce changes in
86 the cell, and eventually in tissue physiology. Some of these molecules have
87 been shown to be important, directly or indirectly, in the development of
88 dermatological diseases. Examples of these are IL-2 and its family, IL-23,
89 interferon alpha,⁵ and IL-17.⁶ The overall pathway has shown its implication in

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5 90 the pathophysiology of diseases such as psoriasis, atopic dermatitis, lupus
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8 91 erythematous, melanoma, or pyoderma gangrenosum.⁷
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11 92 This knowledge has led to the development of drugs that act on the JAK
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13 93 component of the pathway, by selectively inhibiting one (filgotinib, JAK1;
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15 94 pacritinib, JAK2; decernotinib, JAK3) or more than one (tofacitinib, JAK1 y JAK3;
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17 95 ruxolitinib, baricitinib, JAK1 and JAK2) JAK protein.⁸ Ruxolitinib and tofacinib
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19 96 were the first drugs of this class to be approved by the FDA – in 2011 for
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21 97 myelofibrosis and in 2012 for rheumatoid arthritis, respectively.^{9,10}
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25 98 So far, no JAK/STAT inhibitors have been approved a license for the treatment
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27 99 of dermatological diseases. However, evidence exists resulting from the off-
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29 100 label use of these drugs, specifically tofacitinib and ruxolitinib, in different skin
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31 101 diseases. Knowing the efficacy and safety profile of each drug used in different
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33 102 dermatological diseases is essential to establish their risk-benefit balance.
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38 104 Improving knowledge requires ordering evidence, establishing gaps in the
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40 105 evidence, and formulating questions that can be answered using systematic
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42 106 synthesis and analysis techniques. The aim of this is to develop guidelines that
43
44 107 give support to physicians in making effective decisions in clinical practice. For
45
46 108 this purpose, secondary scientific studies can develop methodologies that adapt
47
48 109 to the specific needs of the formulated problem. The application of JAK
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50 110 inhibitors for the treatment of dermatological disorders is still in its early stages,
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52 111 and we consider it necessary to broadly review the knowledge available to date.
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54 112 Otherwise, the conduction of studies aimed at answering specific questions can
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56 113 lead to synthesis efforts that cannot be quantified.¹¹
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8 115 A scope review is a form of scientific synthesis that addresses an exploratory
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10 116 research question, with the aim of mapping key concepts and gaps in research
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12 117 related to a defined area or field.¹² The aim of this protocol was to define the
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14 118 methodology that will be used to broadly synthesize the available evidence on
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17 119 the use of inhibitors of the JAK/STAT pathway in dermatological diseases.
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123 **METHODS**

124 **Protocol design**

125 The aim of the study is to broadly address the published evidence on drugs
126 targeting JAK proteins in the treatment dermatological diseases, for three
127 purposes: a) to structure the existing knowledge in this field; b) to establish
128 areas where there may be gaps in the evidence; c) to formulate new questions
129 that can be answered following the methodology of systematic reviews. With
130 this intention, we used the methodology recently described to conduct scoping
131 reviews.¹³ This methodology outlines a 5-stage approach (**Table 1**): 1) identify
132 the research question; 2) identify relevant studies; 3) select studies; 4) chart the
133 data; and 5) collate, summarize, and report the results, with an optional
134 consultation exercise. Finally, we used the Preferred Reporting Items for
135 Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping
136 Reviews (PRISMA-ScR) to present the results.¹⁴

137

138 **Inclusion criteria**

139 We will use PCC (participants, concept, context) mnemotechnic rule to define
140 the inclusion criteria as follows:

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142 **Participants**

143 All studies that include evidence on the use of JAK protein inhibitors in humans
144 will be included. No restrictions regarding age, ethnicity, study design, or any
145 other characteristics will be made.

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147 **Concept**

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6 148 We will review the existing literature on drugs targeting JAKs proteins in the
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8 149 treatment of dermatological diseases: indications, epidemiology, genetics,
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10 150 efficacy and safety.

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13 14 152 **Context**

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17 153 We will not limit the context to a particular setting or country.

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20 21 155 **Research question**

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24 156 What are the indications, epidemiology, genetics, efficacy, and safety of drugs
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26 157 targeting proteins of STAT/JAK pathway for the treatment of dermatological
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28 158 diseases?

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32 33 160 **Identifying relevant literature**

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35 161 We will perform a three-step literature search. The first step will include an initial
36
37 162 limited search of the MEDLINE and EMBASE databases. Then, we will carry
38
39 163 out analyses of: the text contained in the titles, abstracts of retrieved papers,
40
41
42 164 and the index terms used to describe the articles. In second step, we will search
43
44 165 the same databases using the identified key words and index terms. Thirdly, the
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46 166 reference list of all identified reports and articles will be searched for additional
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49 167 studies. We will contact authors of primary studies or reviews for further
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51 168 information, if relevant. We will include all studies published in English until
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53 169 October 2018. The process will be carried out by at least two researchers.

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57 58 171 **Identifying relevant studies.**

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5 172 We will apply the inclusion criteria, described previously, for the selection of
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12 175 **Charting the data.**

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14 176 We will develop a draft charting to record the information that will be relevant to
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17 177 the review.

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19 178 Questions focusing on:

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21 179 *1) Mapping studies:* Author(s), Year of publication, origin/country of origin
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23 180 (where the study was published or conducted), authors filiation, type of study, a
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25 181 priori design, registration, conflict of interest, funding;

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27 182 *2) Epidemiological and genetics aspects:* Study population and sample size,
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29 183 genetic studies;

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31 184 *3) Evaluation of the efficacy and safety of drugs for each disease:* Intervention
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33 185 type, comparator and details of these, duration of the intervention, dosage,
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35 186 outcomes and details of these and adverse events.

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37 187 The data collection will be done by at least two reviewers.
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44 189 **5. Collating, summarizing and reporting results**

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46 190 The elements of the PCC inclusion criteria will guide the presentation of the
47
48 191 data. Firstly, we will present the results of the search in the PRISMA flow chart.

49
50 192 Secondly, we will organize the extracted data for topics defined as follows:

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52 193 indications, mechanism of action, efficacy safety and cost. For each category, a
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54 194 clear explanation was provided. The results of the scoping review will be

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56 195 presented as a map, in both diagrammatic and tabular form, and in a descriptive
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5 196 format. A narrative summary will accompany the tabulated and/or charted
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8 197 results and will describe how the results relate to the review objective and
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10 198 question(s).

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13 14 200 **6. Differences between the protocol and the overview**

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17 201 Changes in the methodology that need to be carried out throughout the study
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19 202 will be detailed in the results section.

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23 24 204 **Compliance with Ethics Guidelines**

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26 205 This protocol relates to a search for previously conducted studies, and does not
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28 206 involve any new human or animal studies performed by the authors.

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32 33 208 **Patient and Public Involvement**

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35 209 Patients and or public were not involved in the development of this protocol.

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213 **CONCLUSION**

214 Here, we have presented a protocol for systematically conducting a scoping
215 review to broadly analyze the available evidence on the indications for and the
216 mechanisms of action, efficacy, and safety of JAK/STAT pathway-targeting
217 drugs in the use of dermatological therapy. Evidence-based medicine is
218 intended to optimize decision-making by emphasizing the use of evidence
219 derived from well-designed and well-conducted research. Currently, most
220 reviews of treatments blocking the JAK/STAT pathway are narrative reviews,
221 which lack the necessary methodological detail to promote reproducibility and
222 reduce the risk of bias.^{15,16} Secondary research methodologies are constantly
223 being developed and must be adapted to the type of research question being
224 asked and the urgency with which the question must be answered.¹⁷

225 We believe that the scoping review methodology is the one of the best suited
226 protocols to answer the question posed in this study. The results will provide
227 unique insights into the available evidence on the use of JAK/STAT pathway-
228 targeting drugs in the treatment of dermatological diseases, facilitating the
229 detection of knowledge gaps and the identification of new questions to address
230 via additional systematic reviews.

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43 247 **Compliance with Ethics Guidelines.** This protocol relates to a search for
44
45 248 previously conducted studies, and does not involve any new human or animal
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47 249 subjects performed by the authors.
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50 250 **Data sharing statement.** All the original data are presented in the text and
51
52 251 tables of the protocol.
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54
55 252 **Contributors.** FGG and JR conceived the study. FGG, PJGA, JH, AMM, JGM, MAL,
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57 253 IVP, AVGN, BIT, and JR contributed to the protocol design and plan. FGG, PJGA, and
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5 254 JH developed the literature search. All the authors worked collaboratively to draft and
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8 255 revise the manuscript, and read and approved the final version. All the authors made
9
10 256 substantive intellectual contributions to the development of this protocol.
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289 [incytes-jakafitm-ruxolitinib-patients-myelofibrosis](https://investor.incyte.com/news-releases/news-release-details/fda-approves-incytes-jakafitm-ruxolitinib-patients-myelofibrosis)
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319 **TABLES**320 **Table 1.-Stages of the scoping reviews.**

1. Research Question Identified	1.1. Overarching goal	To explore the depth and breadth of evidence for the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of patients with dermatological diseases
	1.2. Research question	What are the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases?
	1.3. Purposes of this scoping review	1.3.1. Review the evidence of indications for drugs that act on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.2. Review the evidence of epidemiology of drugs acting on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.3. Review the evidence of genetics of drugs acting on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.4. Review the evidence on efficacy of the drugs that act on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.5. Review the evidence on safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases

		1.3.6. Obtain concrete research questions that can be answered through a systematic review
		1.3.7. Identify research gaps in the existing literature
2. Identifying relevant literature	2.1. We will perform a three steps-search	2.1.1. First search: an initial limited search of the MEDLINE and EMBASE databases to find keywords in the title, abstract, and the index terms used to describe the articles
		2.1.2. Second search: a search of MEDLINE and EMBASE using all identified keywords
		2.1.3. Third search: the reference lists of all identified reports and articles are searched for additional studies
	2.2. We will include the studies published in full text in English until October 2018	
	2.3. We will contact authors, of primary studies or reviews, for further information, if this is relevant	
	2.4. The search and selection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
3. Selecting studies	3.1. Inclusion criteria	3.1.1. We will include in the review the studies on the human use of drugs inhibitors of JAK/STAT pathway published on the topics: indications, epidemiology, genetics, efficacy, and safety.

		3.1.2. Design of the studies: we will include guidelines, systematic reviews, randomized clinical trials, observational studies, cross sectional case report and series
	3.2. Exclusion criteria	3.2.1. We will exclude narrative reviews and studies performed <i>in vitro</i> or using animal models
4. Charting the data	4.1. We will extract the data in a predefined form.	
	4.2. From each study we will extract title, objective, main variables related to patients, intervention, comparator, outcomes (efficacy and safety) and bibliographic data	
	4.3. We will classify the studies by treatment indication	
	4.4. The list of studies, variables and data of there view will be published in an online-file	
	4.5. The data collection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
5. Collating, summarizing and reporting results	5.1. The results of comprehensive search will be presented using the PRISMA flow diagram	
	5.2. We will synthesize qualitatively the evidence obtained ordering it by topics: indications, mechanism of action, efficacy and safety of drugs that act on	

	JAK/STAT pathway to treat dermatological diseases and we will present it in a diagrammatic tabular form and in a descriptive format	
	5.3. We will use the extension of PRISMA for scoping review for the notification of the review	
6. Differences between the protocol and the overview	Any changes in the methodology that need to be carried out through out the study will be detailed together with the results publication.	

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BMJ Open

Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review

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Keywords:	Protocol, scoping review, JAK/STAT pathway, immune-mediated inflammatory skin diseases, PRISMA

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1 Protocol

2 **BMJ Open**

3 **Title:** Drugs targeting the JAK/STAT pathway for the treatment of immune-
4 mediated inflammatory skin diseases: protocol for a scoping review

5 **Short title:** Scoping review of JAK/STAT blockade in dermatology

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30 ABSTRACT

31 **Introduction.** The JAK/STAT pathway is known to be involved in inflammatory
32 and neoplastic skin diseases, like psoriasis, atopic dermatitis, alopecia areata,
33 vitiligo, and melanoma. Improved knowledge of the components of this pathway
34 has allowed the development of drugs, which act by inhibiting the pathway,
35 blocking specific components. This offers new therapeutic opportunities.
36 Although evidence on the use of JAK/STAT blockades in dermatological
37 diseases is growing, none have been approved for use in treating skin diseases.
38 The aim of this study is to develop an *a priori* protocol to broadly review the
39 available evidence on the use of drugs targeting the JAK/STAT pathway in the
40 treatment of dermatological diseases.

41 **Methods and analysis.** For the conduction of the scoping review protocol, we
42 will employ an established scoping review methodology described in the Joanna
43 Briggs Institute manual. This methodology outlines a 5-stage approach: 1) identify
44 the research question; 2) identify relevant studies; 3) select studies; 4) chart the data;
45 and 5) collate, summarize, and report the results, with an optional consultation exercise.
46 Finally, we will use the Preferred Reporting Items for Systematic Reviews and Meta-
47 Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the
48 results.

49 **Ethics and dissemination.** Since this is a review of the literature, ethics approval is
50 not indicated. We will disseminate the findings from this study in publications in peer-
51 reviewed journals as well as presentations at relevant national and international
52 conferences.

53 **Keywords:** Protocol; scoping review; JAK/STAT pathway; immune-mediated
54 inflammatory skin diseases; PRISMA.

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55 **Article summary**

56 **Strengths and limitations of this study**

- 57 ▪ Strengths of this study include the importance of unrevealing uncertainty about
58 evidence of using drugs targeting JAK/STAT pathway when prescribed as
59 *off-label* for dermatological diseases in the clinical setting.

- 60 ▪ We will use an established scoping review methodology, a systematic search
61 developed by two health sciences librarians, and systematic screening and
62 data abstraction carried out in duplicate.

- 63 ▪ A limitation of this review is the potential to miss relevant articles, especially in
64 the grey literature. To mitigate this, we will screen meeting abstracts to
65 identify any missed articles describing case reports not published in journals
66 and scan reference lists of included articles and similar reviews.

67 INTRODUCTION

68 Improving knowledge of the molecular biology of the cell, and its adaptation to
69 the disease pathogenesis, have allowed the design of new drugs directed
70 against key targets in signaling pathway regulation. In this sense, the Janus
71 kinases (JAKs) and Signal Transducer and Activator of Transcription (STATs)
72 proteins (JAK/STAT) pathway is one of a handful of pleiotropic routes used to
73 transduce multiple extracellular signals involved in cell proliferation,
74 differentiation, migration, and apoptosis.¹ Alterations in the regulation of this
75 process have been associated with pathological events fundamentally related to
76 immunomodulatory and neoplastic (mainly hematological) disorders. In addition,
77 they have been related to the pathophysiology of several dermatological
78 diseases. Therefore, drugs that act on the JAK/STAT pathway represent an
79 opportunity for the treatment of these disorders.²

80 The JAK family is comprised by four types of cytoplasmic tyrosine kinases:
81 JAK1, JAK2, JAK3, and Tyk2.³ STAT, of which there are seven different
82 subtypes (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT 5b, and STAT6), is
83 the other fundamental component of the cascade⁴. After being phosphorylated
84 by JAK, STAT translocates to the nucleus to induce the transcription of specific
85 genes. Different types of ligands, from cytokines, such as interleukins (IL), to
86 hormones, such as erythropoietin, activate this pathway to produce changes in
87 the cell, and eventually in tissue physiology. Some of these molecules have
88 been shown to be important, directly or indirectly, in the development of
89 dermatological diseases. Examples of these are IL-2 and its family, IL-23,
90 interferon alpha,⁵ and IL-17.⁶ The overall pathway has shown its implication in

91 the pathophysiology of diseases such as psoriasis, atopic dermatitis, lupus
92 erythematous, melanoma, or pyoderma gangrenosum.⁷

93 This knowledge has led to the development of drugs that act on the JAK
94 component of the pathway, by selectively inhibiting one (filgotinib, JAK1;
95 pacritinib, JAK2; decernotinib, JAK3) or more than one (tofacitinib, JAK1 and
96 JAK3; ruxolitinib, baricitinib, JAK1 and JAK2) JAK protein.⁸ Ruxolitinib and
97 tofacitinib were the first drugs of this class to be approved by the FDA – in 2011
98 for myelofibrosis and in 2012 for rheumatoid arthritis, respectively.^{9,10}

99 So far, no JAK/STAT inhibitors have been approved a license for the treatment
100 of dermatological diseases. However, evidence exists resulting from the off-
101 label use of these drugs, specifically tofacitinib and ruxolitinib, in different skin
102 diseases. Knowing the efficacy and safety profile of each drug used in different
103 dermatological diseases is essential to establish their risk-benefit balance.

104

105 Improving knowledge requires ordering evidence, establishing gaps in the
106 evidence, and formulating questions that can be answered using systematic
107 synthesis and analysis techniques. The aim of this is to develop guidelines that
108 give support to physicians in making effective decisions in clinical practice. For
109 this purpose, secondary scientific studies can develop methodologies that adapt
110 to the specific needs of the formulated problem. The application of JAK
111 inhibitors for the treatment of dermatological disorders is still in its early stages,
112 and we consider it necessary to broadly review the knowledge available to date.
113 Otherwise, the conduction of studies aimed at answering specific questions can
114 lead to synthesis efforts that cannot be quantified.¹¹

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8 116 A scope review is a form of scientific synthesis that addresses an exploratory
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10 117 research question, with the aim of mapping key concepts and gaps in research
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12 118 related to a defined area or field.¹² The aim of this protocol is to define the
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14 119 methodology that will be used to broadly synthesize the available evidence on
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17 120 the use of inhibitors of the JAK/STAT pathway in dermatological diseases.
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124 **METHODS**

125 **Protocol design**

126 The aim of the study is to broadly address the published evidence on drugs
127 targeting JAK proteins in the treatment dermatological diseases, for three
128 purposes: a) to structure the existing knowledge in this field; b) to establish
129 areas where there may be gaps in the evidence; c) to formulate new questions
130 that can be answered following the methodology of systematic reviews. With
131 this intention, we will use the methodology recently described to conduct
132 scoping reviews.¹³ This methodology outlines a 5-stage approach (**Table 1**): 1)
133 identify the research question; 2) identify relevant studies; 3) select studies; 4)
134 chart the data; and 5) collate, summarize, and report the results, with an
135 optional consultation exercise. Finally, we will use the Preferred Reporting Items
136 for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping
137 Reviews (PRISMA-ScR) to present the results.¹⁴ This protocol is reported
138 following the recommendations of the PRISMA for protocols (PRISMA-P)
139 statement. A checklist for this review protocol has been provided in a
140 Supplementary file.

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142 **Inclusion criteria**

143 We will use PCC (participants, concept, context) mnemotechnic rule to define
144 the inclusion criteria as follows:

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146 **Participants**

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5 147 All studies that include evidence on the use of JAK protein inhibitors in humans
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7 148 will be included. No restrictions regarding age, ethnicity, study design, or any
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9 149 other characteristics will be made.
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15 151 **Concept**

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17 152 We will review the existing literature on drugs targeting JAK proteins in the
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19 153 treatment of dermatological diseases: indications, epidemiology, genetics,
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21 154 efficacy, and safety.
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26 156 **Context**

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28 157 We will not limit the context to a particular setting or country.
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33 159 **Research question**

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35 160 What are the indications, epidemiology, genetics, efficacy, and safety of drugs
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37 161 targeting proteins of STAT/JAK pathway for the treatment of dermatological
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39 162 diseases?
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44 164 **Identifying relevant literature**

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46 165 A systematic search developed by two health sciences librarians will perform
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48 166 using a three-step literature search. The first step will include an initial limited
49
50 167 search of the MEDLINE and EMBASE databases (**Table 2**). Then, we will carry
51
52 168 out analyses of: the text contained in the titles, abstracts of retrieved papers,
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54 169 and the index terms used to describe the articles. In second step, we will search
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56 170 the same databases using the identified key words and index terms.
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171 Additionally, CINAHL, Scopus, and Web of Science to the search engines will
172 be searched in this second step. Thirdly, the reference list of all identified
173 reports and articles will be searched for additional studies. We will contact
174 authors of primary studies or reviews for further information, if relevant. We
175 have established a time frame of four weeks after send authors a mail
176 requesting information about their study or publication. We will include all
177 studies published in English until October 2018. The process of searching,
178 extracting key words, and filtering and excluding studies, will be carried out
179 independently and by duplicate by at least two researchers and in case of
180 disagreement will be decided by agreement with a third reviewer.

181

182 **Identifying relevant studies**

183 We will apply the inclusion criteria, described previously, for the selection of
184 studies. The process will be carried out by at least two researchers and in case
185 of disagreement will be decided by agreement with a third reviewer.

186

187 **Charting the data.**

188 We will develop a draft charting to record the information that will be relevant to
189 the review.

190 Questions focusing on:

191 *1) Mapping studies:* Author(s), Year of publication, origin/country of origin
192 (where the study was published or conducted), authors filiation, type of study, a
193 priori design, registration, conflict of interest, funding;

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5 194 2) *Epidemiological and genetics aspects*: Study population and sample size,
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8 195 genetic studies;

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10 196 3) *Evaluation of the efficacy and safety of drugs for each disease*: Intervention
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12 197 type, comparator and details of these, duration of the intervention, dosage,
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14 198 outcomes and details of these and adverse events.

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17 199 The data collection will be done by at least two reviewers using a piloting
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19 200 customized Google AppSheet form (<https://www.appsheet.com/>) and in case of
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21 201 disagreement will be decided by agreement with a third reviewer. We anticipate
22
23 202 that we can start retrieving data in April 2019 and finalizing by September 2019.

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27 28 204 **5. Collating, summarizing and reporting results**

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30 205 The elements of the PCC inclusion criteria will guide the presentation of the
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32 206 data. Firstly, we will present the results of the search in the PRISMA flow chart.

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35 207 Secondly, we will organize the extracted data for topics defined as follows:

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37 208 indications, mechanism of action, efficacy safety and cost. For each category, a
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39 209 clear explanation will be provided. The results of the scoping review will be
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41 210 presented as a map, in both diagrammatic and tabular form, and in a descriptive
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43 211 format. A narrative summary will accompany the tabulated and/or charted
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45 212 results and will describe how the results relate to the review objective and
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47 213 question(s).

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52 53 215 **6. Differences between the protocol and the overview**

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55 216 Changes in the methodology that need to be carried out throughout the study
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57 217 will be detailed in the results section.

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8 **219 Compliance with Ethics Guidelines**

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10 220 This protocol relates to a search for previously conducted studies, and does not
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12 221 involve any new human or animal studies performed by the authors.
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17 **223 Patient and Public Involvement**

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19 224 Patients and or public were not involved in the development of this protocol.
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7 **228 CONCLUSION**
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10 229 Here, we have presented a protocol for systematically conducting a scoping
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12 230 review to broadly analyze the available evidence on the indications for and the
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14 231 mechanisms of action, efficacy, and safety of JAK/STAT pathway-targeting
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16 232 drugs in the use of dermatological therapy. Evidence-based medicine is
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18 233 intended to optimize decision-making by emphasizing the use of evidence
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20 234 derived from well-designed and well-conducted research. Currently, most
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22 235 reviews of treatments blocking the JAK/STAT pathway are narrative reviews,
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24 236 which lack the necessary methodological detail to promote reproducibility and
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26 237 reduce the risk of bias.^{15,16} Secondary research methodologies are constantly
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28 238 being developed and must be adapted to the type of research question being
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30 239 asked and the urgency with which the question must be answered.¹⁷
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36 240 Although we will try to analyse the quality of evidence per variable and disease
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38 241 using GRADE approach, probably most of the studies have produced
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40 242 documents communicating partial results following an observational design,
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42 243 which is associated with low or very low quality of evidence. However, we
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44 244 believe that the scoping review methodology is the one of the best suited
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46 245 protocols to answer the question posed in this study. The results will provide
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48 246 unique insights into the available evidence on the use of JAK/STAT pathway-
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50 247 targeting drugs in the treatment of dermatological diseases, facilitating the
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52 248 detection of knowledge gaps and the identification of new questions to address
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54 249 via additional systematic reviews.
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265 **Provenance and peer review.** Not commissioned; externally peer reviewed.

266 **Compliance with Ethics Guidelines.** This protocol relates to a search for
267 previously conducted studies, and does not involve any new human or animal
268 subjects performed by the authors.

269 **Data sharing statement.** All the original data are presented in the text and
270 tables of the protocol.

271 **Contributors.** FGG and JR conceived the study. FGG, PJGA, JH, AMM, JGM, MAL,
272 IVG, AVGN, BIT, and JR contributed to the protocol design and plan. FGG, PJGA, and

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5 273 JH developed the literature search strategy. All the authors worked collaboratively to
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8 274 draft and revise the manuscript, and read and approved the final version. All the authors
9
10 275 made substantive intellectual contributions to the development of this protocol. JR is the
11
12 276 guarantor of the review.
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339 **TABLES**

340 **Table 1. Stages of the scoping reviews.**

1. Research Question Identified	1.1. Overarching goal	To explore the depth and breadth of evidence for the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of patients with dermatological diseases
	1.2. Research question	What are the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases?
	1.3. Purposes of this scoping review	1.3.1. Review the evidence of indications for drugs that act on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.2. Review the evidence of epidemiology of drugs acting on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.3. Review the evidence of genetics of drugs acting on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.4. Review the evidence on efficacy of the drugs that act on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.5. Review the evidence on safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases

		1.3.6. Obtain concrete research questions that can be answered through a systematic review
		1.3.7. Identify research gaps in the existing literature
2. Identifying relevant literature	2.1. We will perform a three steps-search	2.1.1. First search: an initial limited search of the MEDLINE and EMBASE databases to find keywords in the title, abstract, and the index terms used to describe the articles
		2.1.2. Second search: a search of MEDLINE and EMBASE using all identified keywords. <i>Additionally, CINAHL, Scopus, and Web of Science to the search engines will be searched in this second step.</i>
		2.1.3. Third search: the reference lists of all identified reports and articles will be searched for additional studies
	2.2. We will include the studies published in full text in English until October 2018	
	2.3. We will contact authors, of primary studies or reviews, for further information, if this is relevant	
	2.4. The search and selection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
3. Selecting studies	3.1. Inclusion criteria	3.1.1. We will include in the review the studies on the human use of drugs inhibitors of JAK/STAT pathway published on the topics: indications, epidemiology, genetics, efficacy, and safety.

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		3.1.2. Design of the studies: we will include guidelines, systematic reviews, randomized clinical trials, observational studies, cross sectional case report and series
	3.2. Exclusion criteria	3.2.1. We will exclude narrative reviews and studies performed <i>in vitro</i> or using animal models
4. Charting the data	4.1. We will extract the data in a predefined form.	
	4.2. From each study we will extract title, objective, main variables related to patients, intervention, comparator, outcomes (efficacy and safety) and bibliographic data	
	4.3. We will classify the studies by treatment indication	
	4.4. The list of studies, variables and data of there view will be published in an online-file	
	4.5. The data collection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
5. Collating, summarizing and reporting results	5.1. The results of comprehensive search will be presented using the PRISMA flow diagram	
	5.2. We will synthesize qualitatively the evidence obtained ordering it by topics: indications, mechanism of action, efficacy and safety of drugs that act on	

	JAK/STAT pathway to treat dermatological diseases and we will present it in a diagrammatic tabular form and in a descriptive format	
	5.3. We will use the extension of PRISMA for scoping review for the notification of the review	
6. Differences between the protocol and the overview	Any changes in the methodology that need to be carried out through out the study will be detailed together with the results publication.	

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Table 2. Draft of first step of search strategy to be used for at least two electronic databases.

MEDLINE (Ovid), Embase (Ovid)

search	
#1	(('tofacitinib' OR 'baricitinib' OR 'ruxolitinib' OR 'oclacitinib' OR 'upadacitinib' OR 'delgocitinib' OR 'itacitinib' OR 'mometinib' OR peficitinib OR 'decernotinib' OR 'fedratinib' OR 'pacritinib' OR 'filgotinib' OR 'gandotinib' OR 'solcitinib' OR 'lestaurtinib' OR 'janus kinase inhibitor')
#2	(('psoriasis'/exp OR psoriasis) OR 'atopic dermatitis' OR 'alopecia' OR 'contact dermatitis' OR 'vitiligo' OR 'graft versus host reaction' OR 'lichen planus' OR 'pyoderma gangrenosum' OR 'pruritus' OR (eosinofilic AND annulare AND erythema) OR 'male type alopecia' OR 'proteasome associated autoinflammatory syndrome' OR 'sting associated vasculopathy with onset in infancy' OR 'chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome' OR 'hand dermatitis' OR 'discoid lupus erythematosus' OR 'mucocutaneous candidiasis' OR (urticaria AND chronic) OR 'suppurative hidradenitis' OR 'melanoma' OR 'non melanoma skin cancer' OR 'acne' OR 'lichen sclerosus et atrophicus' OR 'pityriasis rubra pilaris' OR 'pemphigus' OR 'skin disease' OR 'rosaceae' OR 'scleroderma' OR 'cinca syndrome' OR 'hyperhidrosis' OR 'erythropoietic protoporphyria' OR 'anca associated vasculitis' OR 'seborrheic dermatitis' OR 'herpes simplex' OR 'sjoegren syndrome'))
#3	#1 AND #2

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:		Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review	
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	13,14
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	Table 2

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	NA
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA/11/NA/11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

***It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028303.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Apr-2019
Complete List of Authors:	<p>Gomez-Garcia, Francisco; Hospital Universitario Reina Sofia, Dermatology; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p> <p>Gomez-Arias, Pedro Jesus; Hospital Universitario Reina Sofia, Dermatology; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p> <p>Hernandez, Jorge; Hospital Universitario Reina Sofia, Pharmacy</p> <p>Montilla, Ana Maria; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba; University of Cordoba, School of Medicine</p> <p>Gay-Mimbrera, Jesús; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p> <p>Aguilar-Luque, Macarena; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p> <p>Viguera-Guerra, Isabel; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p> <p>Velez Garcia-Nieto, Antonio; Hospital Universitario Reina Sofia, Dermatology; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p> <p>Isla-Tejera, Beatriz; Hospital Universitario Reina Sofia, Pharmacy; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p> <p>Ruano, Juan; Hospital Universitario Reina Sofia, Dermatology; Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC)/Hospital Universitario Reina Sofia/Universidad de Cordoba</p>
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Immunology (including allergy), Pharmacology and therapeutics
Keywords:	Protocol, scoping review, JAK/STAT pathway, immune-mediated inflammatory skin diseases, PRISMA

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Manuscripts

1 Protocol

2 **BMJ Open**

3 **Title:** Drugs targeting the JAK/STAT pathway for the treatment of immune-
4 mediated inflammatory skin diseases: protocol for a scoping review

5 **Short title:** Scoping review of JAK/STAT blockade in dermatology

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29 29 **World count:** 1,450; **Tables:** 2; **Figures:** 0.
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5 **30 ABSTRACT**

6 **31 Introduction.** The JAK/STAT pathway is known to be involved in inflammatory
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and neoplastic skin diseases, like psoriasis, atopic dermatitis, alopecia areata,
vitiligo, and melanoma. Improved knowledge of the components of this pathway
has allowed the development of drugs, which act by inhibiting the pathway,
blocking specific components. This offers new therapeutic opportunities.
Although evidence on the use of JAK/STAT blockades in dermatological
diseases is growing, none have been approved for use in treating skin diseases.
The aim of this study is to develop an *a priori* protocol to broadly review the
available evidence on the use of drugs targeting the JAK/STAT pathway in the
treatment of dermatological diseases.

41 **Methods and analysis.** For the conduction of the scoping review protocol, we
42 will employ an established scoping review methodology described in the Joanna
43 Briggs Institute manual. This methodology outlines a 5-stage approach: 1) identify
44 the research question; 2) identify relevant studies; 3) select studies; 4) chart the data;
45 and 5) collate, summarize, and report the results, with an optional consultation exercise.
46 Finally, we will use the Preferred Reporting Items for Systematic Reviews and Meta-
47 Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) to present the
48 results.

49 **Ethics and dissemination.** Since this is a review of the literature, ethics approval is
50 not indicated. We will disseminate the findings from this study in publications in peer-
51 reviewed journals as well as presentations at relevant national and international
52 conferences.

53 **Keywords:** Protocol; scoping review; JAK/STAT pathway; immune-mediated
54 inflammatory skin diseases; PRISMA.

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55 **Article summary**

56 **Strengths and limitations of this study**

- 57 ▪ Strengths of this study include the importance of unrevealing uncertainty about
58 evidence of using drugs targeting JAK/STAT pathway when prescribed as
59 *off-label* for dermatological diseases in the clinical setting.

- 60 ▪ We will use an established scoping review methodology, a systematic search
61 developed by two health sciences librarians, and systematic screening and
62 data abstraction carried out in duplicate.

- 63 ▪ A limitation of this review is the potential to miss relevant articles, especially in
64 the grey literature. To mitigate this, we will screen meeting abstracts to
65 identify any missed articles describing case reports not published in journals
66 and scan reference lists of included articles and similar reviews.

67 INTRODUCTION

68 Improving knowledge of the molecular biology of the cell, and its adaptation to
69 the disease pathogenesis, have allowed the design of new drugs directed
70 against key targets in signaling pathway regulation. In this sense, the Janus
71 kinases (JAKs) and Signal Transducer and Activator of Transcription (STATs)
72 proteins (JAK/STAT) pathway is one of a handful of pleiotropic routes used to
73 transduce multiple extracellular signals involved in cell proliferation,
74 differentiation, migration, and apoptosis.¹ Alterations in the regulation of this
75 process have been associated with pathological events fundamentally related to
76 immunomodulatory and neoplastic (mainly hematological) disorders. In addition,
77 they have been related to the pathophysiology of several dermatological
78 diseases. Therefore, drugs that act on the JAK/STAT pathway represent an
79 opportunity for the treatment of these disorders.²

80 The JAK family is comprised by four types of cytoplasmic tyrosine kinases:
81 JAK1, JAK2, JAK3, and Tyk2.³ STAT, of which there are seven different
82 subtypes (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT 5b, and STAT6), is
83 the other fundamental component of the cascade⁴. After being phosphorylated
84 by JAK, STAT translocates to the nucleus to induce the transcription of specific
85 genes. Different types of ligands, from cytokines, such as interleukins (IL), to
86 hormones, such as erythropoietin, activate this pathway to produce changes in
87 the cell, and eventually in tissue physiology. Some of these molecules have
88 been shown to be important, directly or indirectly, in the development of
89 dermatological diseases. Examples of these are IL-2 and its family, IL-23,
90 interferon alpha,⁵ and IL-17.⁶ The overall pathway has shown its implication in

91 the pathophysiology of diseases such as psoriasis, atopic dermatitis, lupus
92 erythematous, melanoma, or pyoderma gangrenosum.⁷

93 This knowledge has led to the development of drugs that act on the JAK
94 component of the pathway, by selectively inhibiting one (filgotinib, JAK1;
95 pacritinib, JAK2; decernotinib, JAK3) or more than one (tofacitinib, JAK1 and
96 JAK3; ruxolitinib, baricitinib, JAK1 and JAK2) JAK protein.⁸ Ruxolitinib and
97 tofacitinib were the first drugs of this class to be approved by the FDA – in 2011
98 for myelofibrosis and in 2012 for rheumatoid arthritis, respectively.^{9,10}

99 So far, no JAK/STAT inhibitors have been approved a license for the treatment
100 of dermatological diseases. However, evidence exists resulting from the off-
101 label use of these drugs, specifically tofacitinib and ruxolitinib, in different skin
102 diseases. Knowing the efficacy and safety profile of each drug used in different
103 dermatological diseases is essential to establish their risk-benefit balance.

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105 Improving knowledge requires ordering evidence, establishing gaps in the
106 evidence, and formulating questions that can be answered using systematic
107 synthesis and analysis techniques. The aim of this is to develop guidelines that
108 give support to physicians in making effective decisions in clinical practice. For
109 this purpose, secondary scientific studies can develop methodologies that adapt
110 to the specific needs of the formulated problem. The application of JAK
111 inhibitors for the treatment of dermatological disorders is still in its early stages,
112 and we consider it necessary to broadly review the knowledge available to date.
113 Otherwise, the conduction of studies aimed at answering specific questions can
114 lead to synthesis efforts that cannot be quantified.¹¹

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8 116 A scope review is a form of scientific synthesis that addresses an exploratory
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10 117 research question, with the aim of mapping key concepts and gaps in research
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12 118 related to a defined area or field.¹² The aim of this protocol is to define the
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14 119 methodology that will be used to broadly synthesize the available evidence on
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17 120 the use of inhibitors of the JAK/STAT pathway in dermatological diseases.
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124 **METHODS**

125 **Protocol design**

126 The aim of the study is to broadly address the published evidence on drugs
127 targeting JAK proteins in the treatment dermatological diseases, for three
128 purposes: a) to structure the existing knowledge in this field; b) to establish
129 areas where there may be gaps in the evidence; c) to formulate new questions
130 that can be answered following the methodology of systematic reviews. With
131 this intention, we will use the methodology recently described to conduct
132 scoping reviews.¹³ This methodology outlines a 5-stage approach (**Table 1**): 1)
133 identify the research question; 2) identify relevant studies; 3) select studies; 4)
134 chart the data; and 5) collate, summarize, and report the results, with an
135 optional consultation exercise. Finally, we will use the Preferred Reporting Items
136 for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping
137 Reviews (PRISMA-ScR) to present the results.¹⁴ This protocol is reported
138 following the recommendations of the PRISMA for protocols (PRISMA-P)
139 statement. A checklist for this review protocol has been provided in a
140 Supplementary file.

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142 **Inclusion criteria**

143 We will use PCC (participants, concept, context) mnemotechnic rule to define
144 the inclusion criteria as follows:

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146 **Participants**

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5 147 All studies that include evidence on the use of JAK protein inhibitors in humans
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8 148 will be included. No restrictions regarding age, ethnicity, study design, or any
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10 149 other characteristics will be made.
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15 151 **Concept**

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17 152 We will review the existing literature on drugs targeting JAK proteins in the
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19 153 treatment of dermatological diseases: indications, epidemiology, genetics,
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21 154 efficacy, and safety.
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26 156 **Context**

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28 157 We will not limit the context to a particular setting or country.
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33 159 **Research question**

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35 160 What are the indications, epidemiology, genetics, efficacy, and safety of drugs
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37 161 targeting proteins of STAT/JAK pathway for the treatment of dermatological
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39 162 diseases?
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44 164 **Identifying relevant literature**

45
46 165 A systematic search developed by two health sciences librarians will perform
47
48 166 using a three-step literature search. The first step will include an initial limited
49
50 167 search of the MEDLINE and EMBASE databases (**Table 2**). Then, we will carry
51
52 168 out analyses of: the text contained in the titles, abstracts of retrieved papers,
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54 169 and the index terms used to describe the articles. In second step, we will search
55
56 170 the same databases using the identified key words and index terms.
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5 171 Additionally, CINAHL, Scopus, and Web of Science to the search engines will
6
7 172 be searched in this second step. Thirdly, the reference list of all identified
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9 173 reports and articles will be searched for additional studies. We will contact
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11 174 authors of primary studies or reviews for further information, if relevant. We
12
13 175 have established a time frame of four weeks after send authors a mail
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15 176 requesting information about their study or publication. We will include all
16
17 177 studies published in English until October 2018. The process of searching,
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19 178 extracting key words, and filtering and excluding studies, will be carried out
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21 179 independently and by duplicate by at least two researchers and in case of
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23 180 disagreement will be decided by agreement with a third reviewer.
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182 **Identifying relevant studies**

183 We will apply the inclusion criteria, described previously, for the selection of
184 studies. The process will be carried out by at least two researchers and in case
185 of disagreement will be decided by agreement with a third reviewer.

186

187 **Charting the data.**

188 We will develop a draft charting to record the information that will be relevant to
189 the review.

190 Questions focusing on:

191 *1) Mapping studies:* Author(s), Year of publication, origin/country of origin
192 (where the study was published or conducted), authors filiation, type of study, a
193 priori design, registration, conflict of interest, funding;

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5 194 2) *Epidemiological and genetics aspects*: Study population and sample size,
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8 195 genetic studies;

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10 196 3) *Evaluation of the efficacy and safety of drugs for each disease*: Intervention
11
12 197 type, comparator and details of these, duration of the intervention, dosage,
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14 198 outcomes and details of these and adverse events.

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17 199 The data collection will be done by at least two reviewers using a piloting
18
19 200 customized Google AppSheet form (<https://www.appsheet.com/>) and in case of
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21 201 disagreement will be decided by agreement with a third reviewer. We anticipate
22
23 202 that we can start retrieving data in April 2019 and finalizing by September 2019.

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27 28 204 **5. Collating, summarizing and reporting results**

29
30 205 The elements of the PCC inclusion criteria will guide the presentation of the
31
32 206 data. Firstly, we will present the results of the search in the PRISMA flow chart.

33
34 207 Secondly, we will organize the extracted data for topics defined as follows:
35
36 208 indications, mechanism of action, efficacy safety and cost. For each category, a
37
38 209 clear explanation will be provided. The results of the scoping review will be
39
40 210 presented as a map, in both diagrammatic and tabular form, and in a descriptive
41
42 211 format. A narrative summary will accompany the tabulated and/or charted
43
44 212 results and will describe how the results relate to the review objective and
45
46 213 question(s).

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50 51 215 **6. Differences between the protocol and the overview**

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54 216 Changes in the methodology that need to be carried out throughout the study
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56 217 will be detailed in the results section.

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8 **219 Ethics and dissemination**
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10 220 This study will analyse only anonymised public data of previously conducted
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12 221 studies, and will not involve any new human or animal studies performed by the
13
14 222 authors. We will prepare the publication in accordance with Preferred Reporting
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16 223 Items for Systematic Reviews and Meta-Analyses guideline and its adaptation
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18
19 224 for scoping reviews. We will publish our findings in peer-reviewed journals and
20
21 225 also may present them at conferences.
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25 **227 Patient and Public Involvement**
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28 228 Patients and or public were not involved in the development of this protocol.
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30 229 The study group developed this study protocol without patient involvement.
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7 **233 CONCLUSION**
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10 234 Here, we have presented a protocol for systematically conducting a scoping
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12 235 review to broadly analyze the available evidence on the indications for and the
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14 236 mechanisms of action, efficacy, and safety of JAK/STAT pathway-targeting
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17 237 drugs in the use of dermatological therapy. Evidence-based medicine is
18
19 238 intended to optimize decision-making by emphasizing the use of evidence
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21 239 derived from well-designed and well-conducted research. Currently, most
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23
24 240 reviews of treatments blocking the JAK/STAT pathway are narrative reviews,
25
26 241 which lack the necessary methodological detail to promote reproducibility and
27
28 242 reduce the risk of bias.^{15,16} Secondary research methodologies are constantly
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30 243 being developed and must be adapted to the type of research question being
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33 244 asked and the urgency with which the question must be answered.¹⁷
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36 245 Although we will try to analyse the quality of evidence per variable and disease
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38 246 using GRADE approach, probably most of the studies have produced
39
40 247 documents communicating partial results following an observational design,
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43 248 which is associated with low or very low quality of evidence. However, we
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45 249 believe that the scoping review methodology is the one of the best suited
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48 250 protocols to answer the question posed in this study. The results will provide
49
50 251 unique insights into the available evidence on the use of JAK/STAT pathway-
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52 252 targeting drugs in the treatment of dermatological diseases, facilitating the
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54 253 detection of knowledge gaps and the identification of new questions to address
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57 254 via additional systematic reviews.
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6

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271 **Compliance with Ethics Guidelines.** This protocol relates to a search for
272 previously conducted studies, and does not involve any new human or animal
273 subjects performed by the authors.

274 **Data sharing statement.** All the original data are presented in the text and
275 tables of the protocol.

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277 IVG, AVGN, BIT, and JR contributed to the protocol design and plan. FGG, PJGA, and

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5 278 JH developed the literature search strategy. All the authors worked collaboratively to
6
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8 279 draft and revise the manuscript, and read and approved the final version. All the authors
9
10 280 made substantive intellectual contributions to the development of this protocol. JR is the
11
12 281 guarantor of the review.
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21 285 license their derivative works on different terms, provided the original work is properly
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314 [incytes-jakafitm-ruxolitinib-patients-myelofibrosis](https://investor.incyte.com/news-releases/news-release-details/fda-approves-incytes-jakafitm-ruxolitinib-patients-myelofibrosis)
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344 **TABLES**345 **Table 1. Stages of the scoping reviews.**

1. Research Question Identified	1.1. Overarching goal	To explore the depth and breadth of evidence for the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of patients with dermatological diseases
	1.2. Research question	What are the indications, epidemiology, genetics, efficacy and safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases?
	1.3. Purposes of this scoping review	1.3.1. Review the evidence of indications for drugs that act on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.2. Review the evidence of epidemiology of drugs acting on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.3. Review the evidence of genetics of drugs acting on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.4. Review the evidence on efficacy of the drugs that act on JAK/STAT pathway in the treatment of dermatological diseases
		1.3.5. Review the evidence on safety of drugs that act on JAK/STAT pathway in the treatment of dermatological diseases

		1.3.6. Obtain concrete research questions that can be answered through a systematic review
		1.3.7. Identify research gaps in the existing literature
2. Identifying relevant literature	2.1. We will perform a three steps-search	2.1.1. First search: an initial limited search of the MEDLINE and EMBASE databases to find keywords in the title, abstract, and the index terms used to describe the articles
		2.1.2. Second search: a search of MEDLINE and EMBASE using all identified keywords. <i>Additionally, CINAHL, Scopus, and Web of Science to the search engines will be searched in this second step.</i>
		2.1.3. Third search: the reference lists of all identified reports and articles will be searched for additional studies
	2.2. We will include the studies published in full text in English until October 2018	
	2.3. We will contact authors, of primary studies or reviews, for further information, if this is relevant	
	2.4. The search and selection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
3. Selecting studies	3.1. Inclusion criteria	3.1.1. We will include in the review the studies on the human use of drugs inhibitors of JAK/STAT pathway published on the topics: indications, epidemiology, genetics, efficacy, and safety.

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		3.1.2. Design of the studies: we will include guidelines, systematic reviews, randomized clinical trials, observational studies, cross sectional case report and series
	3.2. Exclusion criteria	3.2.1. We will exclude narrative reviews and studies performed <i>in vitro</i> or using animal models
4. Charting the data	4.1. We will extract the data in a predefined form.	
	4.2. From each study we will extract title, objective, main variables related to patients, intervention, comparator, outcomes (efficacy and safety) and bibliographic data	
	4.3. We will classify the studies by treatment indication	
	4.4. The list of studies, variables and data of there view will be published in an online-file	
	4.5. The data collection will be done by at least two reviewers and in case of disagreement will be decided by agreement with a third reviewer	
5. Collating, summarizing and reporting results	5.1. The results of comprehensive search will be presented using the PRISMA flow diagram	
	5.2. We will synthesize qualitatively the evidence obtained ordering it by topics: indications, mechanism of action, efficacy and safety of drugs that act on	

	JAK/STAT pathway to treat dermatological diseases and we will present it in a diagrammatic tabular form and in a descriptive format	
	5.3. We will use the extension of PRISMA for scoping review for the notification of the review	
6. Differences between the protocol and the overview	Any changes in the methodology that need to be carried out through out the study will be detailed together with the results publication.	

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Table 2. Draft of first step of search strategy to be used for at least two electronic databases.

MEDLINE (Ovid), Embase (Ovid)

search	
#1	(('tofacitinib' OR 'baricitinib' OR 'ruxolitinib' OR 'oclacitinib' OR 'upadacitinib' OR 'delgocitinib' OR 'itacitinib' OR 'momelotinib' OR peficitinib OR 'decernotinib' OR 'fedratinib' OR 'pacritinib' OR 'filgotinib' OR 'gandotinib' OR 'solcitinib' OR 'lestaurtinib' OR 'janus kinase inhibitor')
#2	(('psoriasis'/exp OR psoriasis) OR 'atopic dermatitis' OR 'alopecia' OR 'contact dermatitis' OR 'vitiligo' OR 'graft versus host reaction' OR 'lichen planus' OR 'pyoderma gangrenosum' OR 'pruritus' OR (eosinofilic AND annulare AND erythema) OR 'male type alopecia' OR 'proteasome associated autoinflammatory syndrome' OR 'sting associated vasculopathy with onset in infancy' OR 'chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome' OR 'hand dermatitis' OR 'discoid lupus erythematosus' OR 'mucocutaneous candidiasis' OR (urticaria AND chronic) OR 'suppurative hidradenitis' OR 'melanoma' OR 'non melanoma skin cancer' OR 'acne' OR 'lichen sclerosus et atrophicus' OR 'pityriasis rubra pilaris' OR 'pemphigus' OR 'skin disease' OR 'rosaceae' OR 'scleroderma' OR 'cinca syndrome' OR 'hyperhidrosis' OR 'erythropoietic protoporphyria' OR 'anca associated vasculitis' OR 'seborrheic dermatitis' OR 'herpes simplex' OR 'sjoegren syndrome'))
#3	#1 AND #2

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:		Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review	
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	NA
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	13,14
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	Table 2

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	NA
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA/11/NA/11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

***It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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